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## Factors Associated with Mortality After Undergoing Thrombectomy for Acute Ischemic Stroke

Hannah Lin

*University of Massachusetts Medical School*

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TITLE PAGE

**FACTORS ASSOCIATED WITH MORTALITY AFTER  
THROMBECTOMY FOR ACUTE ISCHEMIC STROKE**

A Masters Thesis Presented

By

HANNAH LIN, BA

Submitted to the Faculty of the

University of Massachusetts Graduate School of Biomedical Sciences

Worcester, MA 01605

In partial fulfillment of the requirements for the degree of:

MASTER OF SCIENCE

June 12, 2020

BIOMEDICAL SCIENCES

HEALTH SERVICES RESEARCH

## SIGNATURE PAGE

FACTORS ASSOCIATED WITH MORTALITY AFTER  
THROMBECTOMY FOR ACUTE ISCHEMIC STROKE

A Masters Thesis Presented

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HANNAH LIN, BA

The signatures of the Master's Thesis Committee signify  
completion and approval as to style and content of the Thesis

---

Sharina Person PhD, Chair of Committee

---

Arlene Ash PhD, Member of Committee

---

Eric Mick ScD, Member of Committee

---

Feifan Liu PhD, Member of Committee

The signature of the Dean of the Graduate School of Biomedical Sciences signifies that  
the student has met all master's degree graduation requirements of the school.

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Mary Ellen Lane, PhD  
Dean of the Graduate School of Biomedical Sciences

Program:  
Masters of Science in Clinical Investigation

June, 12, 2020

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## ABSTRACT

**Background:** Mechanical thrombectomy is the gold standard for treating patients with certain acute ischemic stroke (AIS) due to large vessel occlusion (LVO). However, even with major advancements and increasing procedural volumes, acute endovascular therapy remains a high-risk procedure with a considerable 90-day mortality rate, affected by a variety of factors.

**Purpose:** To investigate various clinical and procedural factors associated with 90-day mortality in patients undergoing mechanical thrombectomy for emergent treatment of AIS and determine which of these factors made unique contributions to post-thrombectomy prognosis.

**Methods:** We examined a prospective registry of 323 patients treated with endovascular thrombectomy for AIS between 2016 and 2019 at a high-volume comprehensive stroke center in central Massachusetts. We developed two multivariable logistic regression models adjusting for the contributions of baseline characteristics and recanalization parameters, to identify potential predictors of mortality at 90 days.

**Results:** Among 323 AIS patients treated with mechanical thrombectomy, the overall rate of successful recanalization was 86% and the overall post-procedure mortality rate was 29% by 90 days. After univariate analysis, a baseline multivariable model comprised of: history of stroke (OR 0.28, 95% CI 0.09 – 0.68), pre-stroke modified Rankin Scale (*mRS* 2: OR 3.75, 95% CI), severe admission National Institutes of Health Stroke Scale (*NIHSS* 21–42: OR 12.36, 95% CI 1.48 – 103.27), internal carotid artery (ICA) occlusion (OR 2.77, 95% CI 1.18 – 6.55), and posterior circulation occlusion (OR 2.69, 95% CI 1.06 – 6.83) was prognostic of 90-day mortality. A second multivariable model also found the procedural factors of: clot obtained after

each pass (OR 0.49, 95% CI 0.24 – 1.00), successful recanalization (OR 0.21, 95% CI 0.06 – 0.8) and symptomatic intracranial hemorrhage (sICH; OR 17.89, 95% CI 5.22 – 61.29) to be identifiable predictors of post-thrombectomy mortality.

**Conclusion:** Death within 90 days after thrombectomy was increased among patients with higher pre-stroke disability, higher stroke severity on admission, ICA or posterior occlusion, and those with sICH complication. A history of stroke, clot extraction after each device pass, and successful recanalization are associated with decreased 90-day mortality. These identifiable contributors may inform patient selection, prognosis evolution, and shared decision-making regarding emergent thrombectomy for treatment of AIS.

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## CHAPTER I: INTRODUCTION

### *Background*

Despite significant advances in stroke treatment and risk reduction over the past decade, stroke remains the second leading cause of death worldwide and the top source of permanent disability in the United States.<sup>1</sup> The majority (87%) of strokes are ischemic in nature,<sup>2</sup> and between one quarter and one-half of these strokes are due to large vessel occlusions (LVOs).<sup>3-5</sup> These blockages endanger large cerebrovascular territories, are often refractory to intravenous tissue-plasminogen activator (IV t-PA), and are associated with high rates of morbidity and mortality without endovascular intervention.

Several randomized controlled trials (RCTs) have recently demonstrated the effectiveness of new mechanical thrombectomy devices over IV t-PA, bringing about the “endovascular era” of acute ischemic stroke (AIS) treatment.<sup>6-10</sup> Mechanical thrombectomy is now considered the gold standard in treating patients with certain anterior (proximal middle cerebral artery and internal carotid artery) occlusions who present within 6 hours of stroke onset.<sup>6,13</sup> Following evidence from recent RCTs, 2018 national guidelines have extended the recommended operable window to include certain LVO strokes presenting within 24 hours of stroke onset.<sup>11-13</sup> Guidelines have also expanded indications for thrombectomy to include distal cerebral segments and posterior circulation occlusions.

Even with rapidly increasing procedural volumes and overall improved clinical outcomes, emergent thrombectomy remains a challenging and high-risk procedure with a considerable (up to 39%) mortality rate.<sup>15-17</sup> In multi-center registries, approximately 1 in 5 stroke patients who undergo mechanical thrombectomy die within 90 days of the procedure, and many who survive are left with severe disability.<sup>6-7,14</sup> Furthermore, most stroke patients who

undergo mechanical thrombectomy in clinical practice would not have qualified for randomization in the carefully selected arms of the endovascular RCTs, thereby limiting generalizability to many real-world patients with LVO strokes.<sup>18</sup>

### *Objectives*

Not only is there uncertainty regarding the risks and benefits of endovascular therapy in a more generalizable patient population, the factors affecting death after successful thrombectomy are variable. As the indications for mechanical thrombectomy continue to expand, the ability to predict the occurrence of adverse clinical outcomes after endovascular intervention will be important for patient selection, clinical management, and the duration of follow-up. The purpose of this single-center observational study was to examine various clinical and procedural factors associated with 90-day mortality in patients undergoing mechanical thrombectomy for emergent treatment of AIS at a high-volume comprehensive stroke center in central New England. Findings may help clinicians evaluate post-thrombectomy prognosis and identify areas to improve upon thrombectomy-related mortality and complication rates, in the hopes of providing meaningful data to frame shared clinical decision making between physicians, patients, and their families.

## CHAPTER II: STUDY METHODOLOGY

### *Patient Selection*

The Department of Neuro-Interventional Radiology at the University of Massachusetts Medical School (UMMS) maintained a prospective registry of all patients at this institution who were treated with endovascular therapy beginning in 2016. A retrospective analysis was performed on all patients with AIS in the registry who underwent mechanical thrombectomy at this large comprehensive stroke center from June 2016 to August 2019. This single-center observational study was approved by the UMMS Institutional Review Board.

Patients who met the following criteria were included: 1) aged 18 years or older; 2) presented with AIS and LVO of the anterior or posterior circulation; 3) had confirmatory imaging of the target vessel using computed tomography (CT), magnetic resonance imaging (MRI), or angiography; 4) underwent mechanical thrombectomy within 24 hours of stroke symptom onset (i.e., patient's last known well) using stent retrievers or large-bore distal aspiration catheters; and 5) received stent implantation, balloon angioplasty, or intra-arterial rescue therapy in the event of recanalization failure. Patients who had intracranial hemorrhage (ICH) prior to intervention or patients in whom no thrombectomy was attempted due to spontaneous recanalization or IV thrombolysis were excluded. A total of 323 patients met our study inclusion criteria during the period under study.

### *Baseline Variables and Clinical Assessment*

Patients' demographic information, clinical characteristics, and imaging results were prospectively collected from the time of hospital admission to discharge and the 3-month follow-up. Comorbid conditions and 90-day mortality status were extracted from the electronic medical record and confirmed with matching records in the UMMS Data Lake repository.<sup>19</sup> Candidate

risk factors known or hypothesized to be pertinent to stroke morbidity and mortality were abstracted from patient chart review as well, including history of prior stroke or transient ischemic attack (TIA), hypertension, diabetes, hyperlipidemia, coronary artery disease, atrial fibrillation, active smoking, and alcohol use.<sup>14-17</sup> The modified Rankin Scale (mRS) and National Institutes of Health Stroke Scale (NIHSS) were scored upon patients' initial stroke presentation. The mRS is a standard measure of global disability and was used to assess pre-stroke functional status.<sup>20</sup> This integer scale ranges from 0 (no symptoms and total functional independence) to 5 (severe disability requiring nursing care) and 6 (death).<sup>10</sup> The 0 to 42 point NIHSS involved a neurologic exam upon admission that quantified neurologic deficit in the setting of acute stroke. NIHSS was categorized into levels of stroke severity: minor (0-4), moderate (5-15), moderate-to-severe (16-20), and severe (21-42) according to standard classification.<sup>21</sup> The sites of anterior vessel occlusion were divided into the middle cerebral artery (MCA), internal carotid artery (ICA), and ICA-MCA tandem occlusion; sites of posterior circulation occlusion were partitioned into the basilar or posterior cerebral artery (PCA) as confirmed on brain imaging.

### *Endovascular Procedure*

Endovascular therapy was performed under general anesthesia or conscious sedation in the neuro-angiography suite. Mechanical thrombectomy with the newest generation stent retriever system (Trevo or Solitaire) was the first-line approach for achieving recanalization irrespective of IV t-PA use. If multiple passes of the retriever device failed to remove the thrombus, manual aspiration thrombectomy with a reperfusion catheter (Penumbra) was performed. In cases of severe intracranial atherosclerosis or vessel dissection, intracranial balloon angioplasty was performed with or without stenting to preserve restored patency of the occluded segment. Intra-arterial thrombolytics were rarely used to treat distal emboli not

accessible to the device. All treated vessels were examined for significant vasospasm on follow-up angiography after retraction of the stent retriever and treated with intra-arterial verapamil if  $\geq 50\%$  luminal stenosis was found.<sup>22</sup> Further details of these mechanical thrombectomy techniques have been previously described.<sup>22-23</sup>

### *Procedural Measures and Outcome Assessment*

The time from stroke onset to percutaneous groin puncture was recorded at the start of the procedure, marking both the time window of brain ischemia and when thrombectomy was initiated. The time to vessel recanalization (in minutes) was calculated from groin arterial access (time zero) to when blood flow to the target vessel was effectively restored (or time stamp on final CT angiogram if revascularization was not achieved). Other intraprocedural measures assessed included the number of passes attempted with the thrombectomy device and whether or not a clot was obtained after each pass.

The degree of arterial occlusion was assessed after each pass of the device and on the final angiogram according to the modified thrombolysis in cerebral infarction (mTICI) score classification.<sup>24-26</sup> No or incomplete vessel filling was considered recanalization failure, receiving a mTICI grade of 0, 1, or 2A. Successful revascularization status was defined as a mTICI score of 2B (greater than 50% antegrade reperfusion of the occluded artery and its ischemic territory) to 3 (complete reperfusion with normal distal branch filling).<sup>25</sup>

Patients were evaluated for periprocedural complications and adverse events in real time. Serial CT angiography was conducted to detect expansion or resolution of the infarct territory, distal thrombus embolization, and vessel perforation or dissection. All patients underwent a routine post-procedure CT within 12 to 36 hours of thrombectomy to evaluate the presence of intracranial hemorrhage. Symptomatic intracranial hemorrhage (sICH) was defined as a

subarachnoid or intraparenchymal hemorrhage associated with  $\geq 4$  point worsening of NIHSS or  $\geq 1$  point deterioration in level of consciousness. The primary study outcome measure was patient mortality occurring within 90 days following AIS presentation, with death defined as a mRS of 6 and confirmed by patient death date recorded in the EMR.

### *Statistical Analysis*

We examined the association between a number of demographic and clinical prognostic variables with 3 month death rates, comparing patients who survived and died. Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary NC) or StataIC Statistical Software, release 16 (StataCorp LP, College Station, TX). Categorical variables were presented as counts (n) and percentages (%) and compared between patients who had survived or died during the 3 month follow-up period using the chi-square test. Continuous variables were presented as means and standard deviations (SD) or medians and interquartile ranges (IQR) as appropriate, then compared using the independent two-sample t-test. Normality of distributions was assessed using histograms. Candidate factors from Tables 1 and 2 which were hypothesized or previously identified (from literature review and discussion with a neurointerventionalist) as affecting patients' mortality status were entered into univariable logistic regression as covariates (Table 3).

Baseline demographic, clinical, and procedural variables that were clinically relevant and reached a significance threshold of  $p \leq 0.15$  in univariate analyses were considered for subsequent entry into two multivariable logistic regression models. The first multivariable model (Model 1, Table 4) analyzed independent baseline characteristics and was developed using backward selection, with a significance level of  $p \leq 0.05$  for variable retention. The second pre-specified model (Model 2, Table 4) added procedural characteristics to the baseline prognostic

factors identified in Model 1, to examine the combined effect of both baseline and interim thrombectomy variables on 90-day mortality status. Model 2 selected procedural variables meeting  $p \leq 0.05$  significance criteria and allowed for retention of baseline prognosticators not meeting this threshold if they were of particular clinical relevance and consistent with prior literature.<sup>11, 14-17</sup> Model fit was assessed and compared using Akaike's information criterion (AIC).

## CHAPTER III: STUDY RESULTS

### *Patient Characteristics*

Baseline demographic and clinical characteristics of the study population are shown in Table 1. The average age of the study population was  $71.5 \pm 15.5$  years, 50.2% were women, and 82% were of Caucasian race. Among the 323 patients treated with mechanical thrombectomy for AIS, 92 (28.5%) died during the 90 day post-procedural period. Overall, those who died within 90 days post-thrombectomy were significantly older, by an average of 6 years compared with those who survived this high risk period (Table 1). Patients who survived thrombectomy treatment for their LVO stroke were significantly more likely to have had a prior stroke or TIA than those who died. Alcohol use (defined in the medical record as any amount of consumption) was significantly higher in those who survived compared with those who died (Table 1). The rates of other common comorbid medical conditions including hypertension, diabetes, hyperlipidemia, coronary artery disease, and atrial fibrillation were not significantly different between those who survived versus those who died during the 3 month follow-up period.

Patients who died within 90 days had significantly higher pre-stroke mRS disability (mean score 1.4 points vs. 0.7 points,) as well as significantly higher admission NIHSS stroke severity (mean score 20.1 vs. 15.2 points) than those who died (Table 1). A large majority of the treated acute anterior circulation strokes were MCA strokes (220, 77.5%); 35 were ICA strokes and 29 were MCA-ICA occlusions. Of the treated posterior circulation strokes, 23 were due to basilar artery occlusion and 4 were due to PCA occlusions. The proportion of ICA occlusions was nearly double in those who died than in those who were alive 90 days after thrombectomy (16.3% vs. 8.7%,). There was also a higher proportion of posterior circulation strokes in patients who died compared to patients who survived (Table 1).



### *Procedural Characteristics*

Among the 323 patients with a confirmed LVO, less than half (39%) received IV tPA prior to their endovascular procedure. Most patients (86%) who underwent thrombectomy were treated under general anesthesia. Patients who died within 90 days after thrombectomy had an approximate 50 minute longer median stroke onset to groin puncture time compared to patients who survived. It also took longer to recanalize patients who ended up dying within 90 days of the procedure (Table 2).

The need for additional passes (explored as a continuous variable) of the stent-retriever device to extract the thrombus was associated with a significant increase in the 3 month death rate, especially if 3 or more device passes were used. Survivors of thrombectomy were significantly more likely to have had a clot obtained after each device pass (64.1%) than non-survivors (48.9%). Successful recanalization to a mTICI score of 2B or 3 (majority to complete vessel reperfusion) was achieved in 87% of surviving patients and 84% of deceased patients.

Among the patients in whom first-line stent-retriever thrombectomy was attempted, 44 experienced initial recanalization failure requiring rescue angioplasty in the form of balloon dilation or stent implantation and 25 required intra-arterial thrombolytic (t-PA) or anti-platelet therapy (eptifibatide). The need for rescue or intra-arterial therapy during the procedure was not associated with mortality in exploratory or subsequent regression analyses. The 3 month post-procedure survivors experienced significantly fewer intraprocedural complications as well as significantly fewer ICH overall and fewer symptomatic ICH 12 to 36 hours post-thrombectomy compared with those who died during this period (Table 2).

### *Univariate Analysis*

In terms of baseline characteristics, advanced age, a history of prior stroke or TIA, current alcohol use, higher pre-stroke mRS, admission NIHSS, and occlusion site in the ICA were associated with dying within 90 days of thrombectomy intervention for AIS (Table 1). Procedural parameters including the number of device passes, extraction of a clot after each pass, successful recanalization, and intraprocedural complications in the form of ICH or sICH also reached statistical significance in distinguishing survivors from non-survivors of thrombectomy after stroke (Table 2). Variables such as a history of coronary artery disease, posterior circulation occlusion, the time it took to recanalize the vessel, the need for rescue angioplasty or intra-arterial therapy, and the dislodging of distal emboli during the procedure either approached statistical significance or were considered to be clinically relevant. These variables were also included in our univariable logistic regression analyses (Table 3).

### *Multivariable Models*

Two parsimonious models were developed from our multivariable adjusted regression analyses and summarized in Table 4. Categorizing continuous variables (mRS and NIHSS) did not appreciably modify the magnitude of effects found in either model. The first model was built from backward selection of relevant baseline factors only. Model 1 revealed that greater pre-stroke functional disability (*mRS* 2: OR 3.75, 95% CI 1.50 – 9.39; *mRS* 3: OR 3.39, 95% CI 1.55 – 7.42; *mRS* 4: OR 6.25, 95% CI 1.72 – 22.66), severe stroke deficit on admission (*NIHSS* 21–42: OR 12.36, 95% CI 1.48 – 103.27), ICA occlusion (OR 2.77, 95% CI 1.18 – 6.55), and posterior circulation occlusion (OR 2.69, 95% CI 1.06 – 6.83) were associated with post-thrombectomy mortality at 90 days. History of stroke or TIA (OR 0.28, 95% CI 0.09 – 0.68) was inversely associated with mortality at 90 days.

Model 2 combined the influential baseline factors identified in Model 1 with pre-specified procedural characteristics. Clot obtained after each pass (OR 0.49, 95% CI 0.24 – 1.00) and successful recanalization to  $\geq 2B$  (OR 0.21, 95% CI 0.06 – 0.8) were inversely correlated with death at 90 days, while sICH 12 to 36 hours post-procedure (OR 17.89, 95% CI 5.22 – 61.29) was independently associated with mortality after thrombectomy for AIS. The effects of baseline prognostic factors from Model 1 were not substantially changed when procedural parameters were incorporated into Model 2. Pre-stroke functional disability (*mRS* 2: OR 4.43, 95% CI 1.55 – 12.65; *mRS* 3: OR 3.84, 95% CI 1.56 – 9.45; *mRS* 4: OR 5.06, 95% CI 1.09 – 23.51), severe stroke deficit on admission (*NIHSS* 21–42: OR 56.36, 95% CI 1.28 – 999.99, and ICA occlusion (OR 3.28, 95% CI 1.22 – 8.86) retained their statistical significance after multivariable adjustment. Having a history of stroke or TIA (OR 0.27, 95% CI 0.07 – 1.05) or a posterior site of occlusion (OR 1.95, 95% CI 0.65 – 5.83) did not appear to statistically influence the risk of death after thrombectomy in Model 2 after adding procedural variables and holding other baseline variables constant. However, these factors were retained in the second model given their clinical relevance and demonstrated importance with endovascular outcomes.<sup>11, 17, 31,</sup>

<sup>32</sup> The AIC was lower in Model 2 (AIC = 263.4) compared to Model 1 (AIC = 323.3), thus the consideration of procedural variables with baseline characteristics may result in a better fitting and more predictive multivariable model for assessing the risk of dying at 3 months among patients with an AIS undergoing thrombectomy.

**Table 1. Baseline Characteristics of Patients According to Survival Status at 90 Days Post-Thrombectomy**

Characteristic	<u>Alive</u> (n=231)	<u>Died</u> (n=92)	<u>P-Value</u>
<b>Demographic — no. (%)</b>			
<u>Age — mean ± SD:</u>	69.8 ± 15.7	75.8 ± 14.1	0.002*
< 60 years	47 (20.3)	9 (9.8)	0.005*
60 – 69 years	42 (18.2)	28 (30.4)	0.021*
70 – 79 years	76 (32.9)	43 (46.7)	0.019*
≥ 80 years	63 (27.3)	12 (13.0)	0.025*
Sex: Male	120 (51.9)	41 (44.6)	0.22
Race: Caucasian	187 (81.0)	78 (84.8)	0.42
<b>Medical history — no. (%)</b>			
Prior stroke or TIA	35 (15.2)	5 (5.4)	0.017*
Hypertension	134 (58.0)	55 (59.8)	0.83
Diabetes mellitus	50 (21.6)	21 (22.8)	0.85
Hyperlipidemia	82 (35.5)	31 (33.7)	0.76
Coronary artery disease	36 (15.6)	22 (23.9)	0.08
Atrial fibrillation	75 (32.5)	31 (33.7)	0.83
Active smoking	70 (30.3)	30 (32.6)	0.69
Alcohol use	63 (27.3)	14 (15.2)	0.022*
<b>Clinical parameters — no. (%)</b>			
<u>Pre-stroke mRS — mean ± SD:</u>	0.7 ± 1.2	1.4 ± 1.4	<0.001*
No symptoms – mRS 0	144 (62.3)	37 (40.2)	<0.001*
No disability – mRS 1	29 (12.6)	13 (14.1)	0.76
Slight disability – mRS 2	15 (6.5)	14 (15.2)	0.016*
Moderate disability – mRS 3	23 (10.0)	19 (20.7)	0.013*
Moderately severe – mRS 4	7 (3.0)	6 (6.5)	0.16
<u>Admission NIHSS — mean ± SD:</u>	15.2 ± 7.4	20.1 ± 8.4	<0.001*
Minor (NIHSS 0 – 4)	14 (6.1)	2 (2.2)	0.14
Moderate (NIHSS 5 – 15)	98 (42.4)	19 (20.7)	<0.001*
Moderate–Severe (NIHSS 16 – 20)	57 (24.7)	24 (26.1)	0.83
Severe (NIHSS 21 – 42)	52 (22.5)	44 (47.8)	<0.001*
<b>Site of occlusion — no. (%)</b>			
Middle cerebral artery	162 (70.1)	58 (63)	0.22
Internal carotid artery	20 (8.7)	15 (16.3)	0.046*
Tandem MCA–ICA	23 (10.0)	6 (6.5)	0.33
Posterior circulation:	16 (6.9)	11 (12.0)	0.14
Basilar artery	14 (6.1)	9 (9.8)	0.24
Posterior cerebral artery	2 (0.9)	2 (2.2)	0.34

-Values are N (% of Alive or Died), unless otherwise specified as mean ± standard deviation (SD).

-Categorical variables were compared using chi-square test. Continuous variables were compared using student's T-test.

\*Statistically significant. The alpha level for significance for pairwise comparisons was 0.05.

-TIA, transient ischemic attack; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; MCA, middle cerebral artery; ICA, internal carotid artery; PCA, posterior cerebral artery.

**Table 2. Procedural Characteristics of Patients According to Survival Status at 90 Days Post-Thrombectomy**

Characteristic	<u>Alive</u> (n=231)	<u>Died</u> (n=92)	<u>P-Value</u>
<b><i>Pre-treatment characteristics — no. (%)</i></b>			
Intravenous t-PA	89 (38.5)	37 (40.2)	0.88
General anesthesia	198 (85.7)	81 (88.0)	0.42
Stroke onset to groin puncture (min)¶	270 (180.5 – 544)	320 (159 – 564)	0.44
<b><i>Endovascular measures — no. (%)</i></b>			
Number of device passes:¶	1.9 ± 1.1	2.3 ± 1.6	0.010*
1 pass	101 (43.7)	35 (38.0)	0.18
2 passes	57 (24.7)	21 (22.8)	0.54
≥ 3 passes	60 (26.0)	36 (39.1)	0.044*
Clot obtained after each pass	148 (64.1)	45 (48.9)	0.001*
Successful recanalization (≥ 2B)	201 (87.0)	77 (83.7)	<0.001*
Time to recanalization (min)¶	50 (31 – 83)	56.5 (36.5 – 83.5)	0.15
Rescue angioplasty†	30 (13.0)	14 (15.2)	0.60
Intra-arterial therapy‡	20 (8.7)	5 (5.4)	0.33
<b><i>Periprocedural adverse events — no. (%)</i></b>			
Any procedural complication:	59 (25.5)	44 (47.8)	<0.001*
Distal embolization	21 (9.1)	9 (9.8)	0.85
Any intracranial hemorrhage	40 (17.3)	33 (35.9)	<0.001*
Symptomatic ICH§	4 (1.7)	27 (29.3)	<0.001*

Values are N (% of Alive or Died), unless otherwise specified as: ¶mean ± standard deviation (SD) or ¶median interquartile range (IQR). Categorical variables were compared using chi-square test. Continuous variables were compared using student's T-test.

\*Statistically significant. The alpha level for significance for pairwise comparisons was 0.05.

-IV t-PA, intravenous tissue-plasminogen activator; mTICI denotes modified Treatment in Cerebral Ischemia classification, with scores ranging from 0 (no flow) to 3 (normal flow). Recanalization was defined as a TICI score of 2B or 3 (≥50% or complete restoration of flow at the site of arterial occlusion.)

†Techniques included balloon dilation and stent implantation.

‡Intra-arterial thrombolytics (t-PA) or anti-platelet therapy (eptifibatide)

§Symptomatic intracerebral hemorrhage (ICH) was defined as subarachnoid or intraparenchymal hemorrhage at 12–36 hours associated with ≥ 4 point worsening of NIHSS or ≥ 1 point deterioration in level of consciousness.

**Table 3. Univariate Logistic Regression of Characteristics Associated with 90-Day Mortality**

<i>Variable</i>	<i>OR</i>	<i>95% CI</i>
<b>Baseline Characteristics</b>		
<i>Age:</i>		
60 – 69 years*	1.01	0.39 – 2.58
70 – 79 years*	3.50	1.60 – 7.64
≥ 80 years*	2.97	1.44 – 6.11
<i>Medical history:</i>		
Prior stroke or TIA	0.32	0.12 – 0.85
Coronary artery disease	1.70	0.94 – 3.09
Alcohol use	0.48	0.25 – 0.91
<i>Pre-stroke mRS score:</i>		
No disability – mRS 1†	1.75	0.83 – 3.68
Slight disability – mRS 2†	3.63	1.61 – 8.19
Moderate disability – mRS 3†	3.22	1.59 – 6.52
Moderately severe – mRS 4†	3.34	1.06 – 10.52
<i>Admission NIHSS score:</i>		
Moderate (NIHSS 5 – 15)‡	1.36	0.29 – 6.46
Moderate–Severe (NIHSS 16 – 20)‡	2.95	0.62 – 13.97
Severe (NIHSS 21 – 42)‡	5.92	1.28 – 27.49
<i>Site of occlusion:</i>		
Internal carotid artery	2.06	1.00 – 4.22
Posterior circulation	1.83	0.81 – 4.10
<b>Procedural Characteristics</b>		
<i>Number of device passes:</i>		
2 passes**	1.06	0.57 – 2.00
≥ 3 passes**	1.73	0.99 – 3.05
<i>Endovascular measures:</i>		
Clot obtained after each pass	0.41	0.25 – 0.68
Successful recanalization (≥ 2B)‖	0.20	0.08 – 0.50
Time to recanalization (hours)	1.21	0.93 – 1.58
Rescue angioplasty††	1.20	0.61 – 2.39
Intra-arterial therapy‡‡	0.61	0.22 – 1.67
<i>Periprocedural adverse events:</i>		
Any procedural complication	2.73	1.65 – 4.53
Distal emboli during procedure	1.08	0.48 – 2.47
Any intracranial hemorrhage	2.67	1.55 – 4.61
Symptomatic ICH§	23.57	7.96 – 69.81

-Crude odds ratios (ORs) were estimated from univariate logistic regression: Adjusted odds ratios (ORs) were estimated from multivariable logistic regression: ORs estimate the relative odds of death within 90 days among patients with or without the factor shown, except where other categories are indicated.

-CI, confidence interval; TIA, transient ischemic attack; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; ICA, internal carotid artery.

†Pre-stroke mRS score: vs. mRS score 0, defined as no symptoms and total functional independence.

‡Admission NIHSS score: vs. minor NIHSS score (0–4), defined as subclinical to minimal neurologic deficits.

\*Age: vs. < 60 years. \*\*Number of device passes: vs. 1 pass of thrombectomy stent–retriever device.

‖Successful recanalization was defined as achieving a TICI score of 2B or 3 ( $\geq 50\%$  or complete restoration of flow occlusion). ††Techniques included balloon dilation and stent implantation.

‡‡Intra-arterial thrombolytics (t-PA) or anti-platelet therapy (eptifibatide).

§Symptomatic intracerebral hemorrhage (ICH) was defined as subarachnoid or intraparenchymal hemorrhage at 12–36 hours associated with  $\geq 4$  point worsening of NIHSS or  $\geq 1$  point deterioration in level of consciousness.

**Table 4. Multivariable Analysis of Factors Associated with 90-Day Mortality**

Variable	<b>Model 1<sup>1</sup></b>		<b>Model 2<sup>2</sup></b>	
	OR	95% CI	OR	95% CI
Prior stroke or TIA	0.28	0.09 – 0.68	0.27	0.07 – 1.05
Pre-stroke mRS 1†	2.06	0.91 – 4.69	3.05	1.21 – 7.7
Pre-stroke mRS 2†	3.75	1.50 – 9.39	4.43	1.55 – 12.65
Pre-stroke mRS 3†	3.39	1.55 – 7.42	3.84	1.56 – 9.45
Pre-stroke mRS 4†	6.25	1.72 – 22.66	5.06	1.09 – 23.51
Admission NIHSS 5–15‡	2.83	0.33 – 24.36	8.97	0.21 – 388.48
Admission NIHSS 16–20‡	6.12	0.72 – 52.29	20.61	0.47 – 907.26
Admission NIHSS 21–42‡	12.36	1.48 – 103.27	56.36	1.28 – 999.99
ICA occlusion	2.77	1.18 – 6.55	3.28	1.22 – 8.86
Posterior occlusion	2.69	1.06 – 6.83	1.95	0.65 – 5.83
Clot obtained after each pass	—	—	0.49	0.24 – 1.00
Successful recanalization ( $\geq 2B$ )	—	—	0.21	0.06 – 0.80
Symptomatic ICH§	—	—	17.89	5.22 – 61.29

<sup>1</sup>Model 1 was developed using backward selection of only baseline characteristics, with a significance level of  $p \leq 0.05$  for variable retention. Akaike information criterion (AIC) = 323.3 <sup>2</sup>Model 2 was pre-specified to include baseline prognostic factors from Model 1 and clinically relevant procedural characteristics. AIC = 263.4

-Adjusted odds ratios (ORs) were estimated from multivariable logistic regression: ORs estimate the relative odds of death within 90 days among patients with or without the factor shown, except where other categories are indicated.

-CI, confidence interval. TIA, transient ischemic attack; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; ICA, internal carotid artery; Successful recanalization was defined as achieving a TICI score of 2B or 3 ( $\geq 50\%$  or complete restoration of flow at the site of arterial occlusion).

†Pre-stroke mRS score: vs. mRS score 0, defined as no symptoms and total functional independence.

‡Admission NIHSS score: vs. minor NIHSS score (0–4), defined as subclinical to minimal neurologic deficits.

§Symptomatic intracerebral hemorrhage (ICH) was defined as subarachnoid or intraparenchymal hemorrhage at 12–36 hours associated with  $\geq 4$  point worsening of NIHSS or  $\geq 1$  point deterioration in level of consciousness.



## CHAPTER IV: DISCUSSION

This study analyzed a variety of prognostic factors associated with 90-day mortality after emergent mechanical thrombectomy among patients with an acute LVO stroke. The overall mortality rate during the 90 day post-procedural period for this study population was 28.5%, which is comparable to findings in prior registry studies with similar study design and inclusion criteria.<sup>8, 11, 17, 30-32</sup> Major findings from multivariable modeling showed that the baseline characteristics of pre-stroke mRS score, admission NIHSS, history of stroke or TIA, ICA occlusion, and posterior occlusion were independent indicators of mortality, baseline functional and stroke severity scores remained important when combined with procedural parameters, and clot extraction after each pass, successful recanalization, and sICH post-procedure were also independently associated with an increased or decreased risk of dying after endovascular intervention.

### *Admission NIHSS*

High admission NIHSS (21 – 42), specifically in the score range classified as severe stroke, was independently associated with increased mortality by 3 month follow-up. This finding was consistent with several studies. Both Linfante and Gory et al. reported high NIHSS on admission to be predictive of mortality at 3 months despite successful recanalization.<sup>14, 17</sup> Shi et al. also reported baseline NIHSS score to be an independent predictor of functional dependence (mRS 3-6) despite successful revascularization.<sup>33</sup> These consistent findings demonstrate the difficulty of reversing a severe neurological deficit at stroke onset even with immediate and successful endovascular reperfusion. However, a high NIHSS at presentation should not be used to exclude patients from thrombectomy eligibility, because patients with severe NIHSS scores

have even worse outcomes with IV t-PA and medical management alone than with endovascular therapy.<sup>8, 10, 33</sup>

### *Pre-stroke mRS*

Similar to stroke severity, pre-stroke mRS was another baseline characteristic that was independently associated with 90-day mortality in this study. The estimated effect of baseline functional status on risk of death also increased as the mRS disability score increased. This is a novel finding, as a graded association between pre-stroke functional dependence and risk of post-thrombectomy mortality has not been reported previously. These results show the importance of considering not just stroke severity and neurologic deficits through NIHSS, but also assessing baseline global functioning when determining which stroke patients may benefit from stent-retriever thrombectomy.

### *History of Stroke or TIA*

Surprisingly, a history of previous stroke or TIA was inversely associated with mortality in this study and may have a protective effect on post-thrombectomy outcomes. Yoon et al. found the opposite association, in which mortality occurred more frequently in patients with previous stroke or TIA than those with no cerebrovascular history.<sup>31</sup> Prior stroke or TIA was found as a predictor of both short-term and long-term mortality in AIS patients compared to healthy controls in other observational studies.<sup>34, 35</sup> In contrast, both Awad and Sharobeam et al. reported that having a prior stroke or TIA was not a significant factor in poor outcomes after thrombectomy for AIS.<sup>36-37</sup> Bousslama et al. observed that repeated mechanical thrombectomy in patients with a recurrent history of LVO stroke was both safe and feasible.<sup>38</sup>

A possible explanation for our unique findings on the protective association of recurrent stroke or TIA may be that having survived a prior AIS is a proxy for good collateral circulation.

Adequate collateral perfusion has been correlated with LVO strokes that are asymptomatic or produce only minimal neurologic deficits.<sup>39</sup> Future research is needed to clarify the utility and prognosis of thrombectomy for patients with a history of stroke and to better manage vascular risk factors for preventing recurrent stroke.

### *ICA and Posterior Circulation Occlusions*

We found that vessel occlusions located in the ICA and posterior circulation were associated with increased death within 90 days of endovascular treatment. Site of occlusion in the ICA retained significance in multivariable analyses of both baseline and procedural characteristics, while LVO located in the posterior arteries no longer influenced mortality when procedural parameters were accounted for in the model. This was likely due to the study being underpowered to detect significant differences, with few cases of posterior circulation strokes overall. Specifically, basilar artery occlusions account for 5% of LVOs, yet are associated with 68% to 78% severe disability and mortality in studied patients treated with mechanical thrombectomy.<sup>40</sup> The frequency of this dismal prognosis has led to basilar artery occlusions often being referred to as the “orphan” of LVOs.<sup>40</sup>

Similar to posterior occlusions, acute ICA occlusions have been associated with poor outcomes.<sup>14, 17</sup> This correlation may be due to high initial infarct volumes in proximally occluded vessels and technical challenges in recanalizing ICA occlusions.<sup>14</sup> Patients with posterior and ICA strokes were initially excluded from the landmark endovascular RCTs.<sup>6-11</sup> However, angioplasty and stenting of these types of occlusions have resulted in favorable clinical outcomes,<sup>14</sup> leading to thrombectomy now being recommended for certain acute presentations of vertebrobasilar and ICA strokes. These collective findings substantiate the need for the inclusion

of ICA and posterior occlusion strokes in future trials, to elucidate the relationship between anatomical site and prognosis as well as improve upon thrombectomy outcomes.

### *Successful Recanalization and Clot Extraction*

Several prior studies using older generation stent retriever devices have found recanalization status (as classified by the TICI scoring system) to be a strong indicator of prognosis and clinical outcomes.<sup>11, 14, 17, 31</sup> The present study using the newest generation devices is consistent with these results. Successful recanalization to a mTICI score of 2B ( $\geq 50\%$  reperfusion) or greater continues to be inversely associated with mortality after thrombectomy. Recent studies have shown that achieving complete restoration of blood flow to a mTICI score of 3 resulted in reduced infarct growth and greater post-thrombectomy functional independence than revascularization only to 2B.<sup>41</sup> Future research on AIS patients undergoing endovascular therapy should explore whether successful recanalization should be redefined as achieving a mTICI 3 score. A unique surgical parameter not evaluated in other studies was whether part or all of the clot was obtained from each pass of the stent retriever. We found that a clot yielded after each pass of the device was marginally and inversely associated with death at 90 days. This slight protective effect considers the benefit of optimizing surgical techniques and warrants further exploration of more efficient technical strategies.

### *Symptomatic Intracranial Hemorrhage*

Finally, the periprocedural complication of symptomatic ICH 12 to 36 hours after mechanical thrombectomy demonstrated the strongest association with 90-day mortality after thrombectomy in multivariable analysis. This was in direct contrast to Gory's observations that procedure-related adverse events and occurrence of ICH were not correlated with death.<sup>17</sup> However, our results were consistent with other single and multi-center study findings

supporting that parenchymal ICH was associated with higher rates of mortality and poor outcome.<sup>11, 31</sup> ICH can result from reperfusion injury after prolonged ischemia or can occur due to vessel wall perforation as a technical complication of the endovascular procedure.<sup>36</sup> Thus, sICH is a strong prognosticator of post-thrombectomy death that is potentially modifiable by either shortening the amount of time it takes to receive endovascular treatment or by improving intraprocedural techniques to prevent fatal operator-induced brain bleeds.

### *Study Strengths and Limitations*

Findings of this study reveal several important associations and potential prognosticators for 90-day mortality after thrombectomy for AIS. However, there are some limitations that need to be considered in this single center observational study. First, this was an unsponsored non-randomized registry study limited by its retrospective design. The single-center design and mostly Caucasian study population may limit generalizability of the results. Given the sparsity of available thrombectomy intervention overall for AIS patients with LVO, this study had a considerable and greater sample size relative to most endovascular stroke trials.<sup>8-12</sup> Despite the high volume of study patients treated at this comprehensive stroke center, we may still have been underpowered to detect certain significant differences.

This study analyzed many unique factors for influence on mortality after endovascular intervention, however we did not evaluate baseline blood glucose. Blood glucose levels at admission have been associated with mortality following stent-retriever thrombectomy and thus may have been a potential confounder that was unaccounted for.<sup>11, 30</sup> Due to incomplete availability of radiographic images from patients transferred from outside facilities, the Alberta Stroke Program Early CT Score (ASPECTS) score at presentation was also not consistently assessed. Although unfavorable ASPECTS scores have been associated with poor functional

outcomes in prior studies, the score is limited to the anterior circulation.<sup>27, 28</sup> There is also disagreement over the methodological constraints and utility of ASPECTS in predicting 90-day mortality.<sup>29</sup> Future large prospective multi-center studies evaluating novel and aforementioned factors are needed to validate the present findings, predict prognosis at varying time points after undergoing thrombectomy, and improve outcomes in emergent endovascular intervention for patients with AIS.

### *Conclusion*

Although recent advances in endovascular therapy have improved patient prognosis and continue to expand the utility of mechanical thrombectomy for patients with acute stroke, a considerable proportion of patients die during a relatively short follow-up. Mortality after successful thrombectomy is multifactorial, as evidenced by varied and conflicting findings in previous reports. Multivariable analyses of the present study findings revealed that pre-stroke mRS, admission NIHSS, history of stroke or TIA, ICA or posterior occlusion, high-yield clot extraction per pass, successful recanalization, and post-procedure sICH are independent factors associated with 90-day mortality after thrombectomy for AIS. These findings may differentiate patients who are more suited for endovascular intervention, inform prognosis evaluation, and help guide shared decision-making on mechanical thrombectomy for LVO stroke. Further research is needed to reach a consensus on risk-adjustable factors and modifiable procedural characteristics to better select candidates for thrombectomy and improve upon endovascular treatment of acute ischemic stroke.

## **Glossary of Abbreviations**

AIC Akaike's information criterion

AIS acute ischemic stroke

ASPECTS Alberta Stroke Program Early CT Score

CT computed tomography

ICA intracranial internal carotid artery

ICH intracranial hemorrhage

IQR interquartile ranges

IA intraarterial

IV intravenous

LVO large vessel occlusions

MCA middle cerebral arteries

MRI magnetic resonance imaging

mRS modified Rankin Scale

mTICI modified thrombolysis in cerebral infarction

NIHSS National Institutes of Health Stroke Scale

PCA posterior cerebral artery

RCT randomized controlled trial

sICH symptomatic intracranial hemorrhage

SD standard deviation

TIA transient ischemic attack

t-PA tissue-plasminogen activator

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